ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG 6,000 units
Powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG 6,000 units
1 vial contains 6,000 units (30 mg) tenecteplase.
1 prefilled syringe contains 6 ml water for injections.

The reconstituted solution contains 1,000 units (5 mg) tenecteplase per ml.

Potency of tenecteplase is expressed in units (U) by using a reference standard which is specific for tenecteplase and is not comparable with units used for other thrombolytic agents.

Tenecteplase is a recombinant fibrin-specific plasminogen activator.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

The powder is white to off-white.

The reconstituted preparation results in a colourless to pale yellow, clear solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG is indicated for the thrombolytic treatment of suspected myocardial infarction with persistent ST elevation or recent left Bundle Branch Block within 6 hours after the onset of acute myocardial infarction (AMI) symptoms.

4.2 Posology and method of administration

Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG should be prescribed by physicians experienced in the use of thrombolytic treatment and with the facilities to monitor that use.

Treatment with Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG should be initiated as soon as possible after onset of symptoms.

Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG should be administered on the basis of body weight, with a maximum dose of 10,000 units (50 mg tenecteplase). The volume required to administer the correct dose can be calculated from the following scheme:

Patients' body weight category (kg)	Tenecteplase (U)	Tenecteplase (mg)	Corresponding volume of reconstituted solution (ml)
< 60	6,000	30	6
≥ 60 to < 70	7,000	35	7
≥ 70 to < 80	8,000	40	8
≥ 80 to < 90	9,000	45	9
≥ 90	10,000	50	10
See section 6.6.: Instructions for use and handling			

The required dose should be administered as a single intravenous bolus over approximately 10 seconds.

A pre-existing intravenous line may be used for administration of Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG in 0.9% sodium chloride solution only. Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG is incompatible with dextrose solution.

No other medicinal product should be added to the injection solution.

Adjunctive therapy
Acetylsalicylic acid (ASA) and heparin should be administered as soon as possible after diagnosis to inhibit the thrombogenic process.

ASA should be administered as soon as possible after AMI symptom onset and continued as long-term treatment. The recommended initial oral dose is between 150 and 325 mg per day. If the patient is unable to ingest tablets, an initial dose of 100-250 mg may be given intravenously if available. The ASA dosage during the following days will be at the discretion of the treating physician.

Heparin should be administered as soon as possible after the diagnosis of AMI has been confirmed, and continued for at least 48 hours on a body weight adjusted basis. For patients weighing 67 kg or less, an initial intravenous heparin bolus not exceeding 4,000 IU is recommended followed initially by not more than an 800 IU/hour infusion. For patients weighing more than 67 kg, an initial intravenous heparin bolus not exceeding 5,000 IU is recommended followed initially by not more than 1,000 IU/hour infusion. For patients already receiving heparin treatment, the initial bolus should not be given. The infusion rate should be adjusted to maintain an aPTT of 50-75 seconds (1.5 to 2.5 times control or a heparin plasma level of 0.2 to 0.5 IU/ml).

4.3 Contraindications

Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG is contraindicated in the following situations because thrombolytic therapy is associated with a higher risk of bleeding:

- Significant bleeding disorder either at present or within the past 6 months
- Patients with current concomitant oral anticoagulant therapy (INR > 1.3)
- Any history of central nervous system damage (i.e. neoplasm, aneurysm, intracranial or spinal surgery)
- Known haemorrhagic diathesis
- Severe uncontrolled hypertension
- Major surgery, biopsy of a parenchymal organ, or significant trauma within the past 2 months
- (this includes any trauma associated with the current AMI)
- Recent trauma to the head or cranium
- Prolonged cardiopulmonary resuscitation (> 2 minutes) within the past 2 weeks
- Acute pericarditis and/or subacute bacterial endocarditis
- Acute pancreatitis

- Severe hepatic dysfunction, including hepatic failure, cirrhosis, portal hypertension (oesophageal varices) and active hepatitis
- Diabetic haemorrhagic retinopathy or other haemorrhagic ophthalmic conditions
- Active peptic ulceration
- Arterial aneurysm and known arterial/venous malformation
- Neoplasm with increased bleeding risk
- Any known history of stroke or transient ischaemic attack or dementia
- Hypersensitivity to the active substance tenecteplase and to any of the excipients

4.4 Special warnings and special precautions for use

Bleeding
The most common complication encountered during Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG therapy is bleeding. The concomitant use of heparin anticoagulation may contribute to bleeding. As fibrin is lysed during Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG therapy, bleeding from recent puncture site may occur. Therefore, thrombolytic therapy requires careful attention to all possible bleeding sites (including catheter insertion sites, arterial and venous puncture sites, cutdown sites and needle puncture sites). The use of rigid catheters as well as intramuscular injections and non-essential handling of the patient should be avoided during treatment with Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG.

Most frequently haemorrhage at the injection site, and occasionally genitourinary and gingival bleeding were observed.

Should serious bleeding occur, in particular cerebral haemorrhage, concomitant heparin administration should be terminated immediately. Administration of protamine should be considered if heparin has been administered within 4 hours before the onset of bleeding. In the few patients who fail to respond to these conservative measures, judicious use of transfusion products may be indicated. Transfusion of cryoprecipitate, fresh frozen plasma, and platelets should be considered with clinical and laboratory reassessment after each administration. A target fibrinogen level of 1 g/l is desirable with cryoprecipitate infusion. Antifibrinolytic agents are available as a last alternative. The use of Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG therapy has to be carefully evaluated in order to balance the potential risks with anticipated benefits under the following conditions:

- Systolic blood pressure > 160 mm Hg
- Cerebrovascular disease
- Recent gastrointestinal or genitourinary bleeding (within the past 10 days)
- High likelihood of left heart thrombus, e.g., mitral stenosis with atrial fibrillation
- Any known recent (within the past 2 days) intramuscular injection
- Advanced age, i.e. over 75 years
- Low body weight < 60 kg

Arrhythmias
Coronary thrombolysis may result in arrhythmias associated with reperfusion. It is recommended that antiarrhythmic therapy for bradycardia and/or ventricular tachyarrhythmias (pacemaker, defibrillator) be available when Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG is administered.

GPIIb/IIIa antagonists
There is no experience with the use of GPIIb/IIIa antagonists within the first 24 hours after start of treatment.

Re-administration
Since at present there is no experience with re-administration of Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG, the re-administration is not recommended. However, no antibody formation to the tenecteplase molecule has been observed. If an anaphylactoid reaction occurs, the injection should be discontinued immediately and appropriate therapy should be initiated. In any case,

tenecteplase should not be re-administered before assessment of haemostatic factors like fibrinogen, plasminogen and alpha2-antiplasmin.

4.5 Interaction with other medicinal products and other forms of interaction

No formal interaction studies with Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG and medicinal products commonly administered in patients with AMI have been performed. However, the analysis of data from more than 12,000 patients treated during phase I, II and III did not reveal any clinically relevant interactions with medicinal products commonly used in patients with AMI and concomitantly used with Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG.

Medicinal products that affect coagulation or those that alter platelet function (e.g. ticlopidine, clopidogrel, LMWH) may increase the risk of bleeding prior to, during or after Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG therapy.

4.6 Pregnancy and lactation

No experience in pregnant women is available for tenecteplase. Because animal studies (see also section 5.3.) have shown a high risk of vaginal bleeding presumably from the placenta and of pregnancy loss, the benefit of treatment has to be evaluated against the potential risks which may aggravate an acute life-threatening situation.

It is not known if tenecteplase is excreted into breast milk. Breast milk should be discarded within the first 24 hours after thrombolytic therapy.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Haemorrhage
Haemorrhage is a very common undesirable effect associated with the use of tenecteplase. The type of haemorrhage is predominantly superficial at the injection site. Ecchymoses are observed commonly but usually do not require any specific action. Commonly, (< 10%) gastro-intestinal or genitourinary bleeding and epistaxis occurred. Pulmonary haemorrhage, retroperitoneal bleedings and cerebral haemorrhage were uncommonly observed (< 1%). Haemopericardium occured rarely. Death and permanent disability are reported in patients who have experienced stroke (including intracranial bleeding) and other serious bleeding episodes. Blood transfusions were rarely required.

Cardiovascular
As with other thrombolytic agents, the following events have been reported as sequelae of myocardial infarction and/or thrombolytic administration:

- very common (>10%): hypotension, heart rate and rhythm disorders, angina pectoris
- common (>1%, <10%): recurrent ischaemia, heart failure, reinfarction, cardiogenic shock, pericarditis, pulmonary oedema
- uncommon (>0.1%, <1%): cardiac arrest, mitral insufficiency, pericardial effusion, venous thrombosis, cardiac tamponade, myocardial rupture
- rare (>0.01%, <0.1%): pulmonary embolism

Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG therapy may lead to crystal cholesterol embolisation in very rare cases or uncommonly to thrombotic embolism.

These cardiovascular events can be life-threatening and may lead to death.

Nervous system
Isolated cases of events related to the nervous system (e.g. somnolence, aphasia, convulsion) have been reported. Ischaemic or haemorrhagic cerebrovascular events may be contributing or underlying conditions.

Anaphylactoid Reaction
Anaphylactoid reactions (e.g. rash, urticaria, laryngeal oedema) have been rarely reported.

Other
Nausea and/or vomiting and fever were commonly reported and are most frequent of the remaining adverse events.

4.9 Overdose

In the event of overdose there may be an increased risk of bleeding. In case of severe prolonged bleeding substitution therapy may be considered (plasma, platelets), see also section 4.4.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antithrombotic agents, ATC code: B01A D

Mechanism of action
Tenecteplase is a recombinant fibrin-specific plasminogen activator that is derived from native t-PA by modifications at three sites of the protein structure. It binds to the fibrin component of the thrombus (blood clot) and selectively converts thrombus-bound plasminogen to plasmin, which degrades the fibrin matrix of the thrombus. Tenecteplase has a higher fibrin specificity and greater resistance to inactivation by its endogenous inhibitor (PAI-1) compared to native t-PA.

Pharmacodynamic effects
After administration of tenecteplase dose dependent consumption of α2-antiplasmin (the fluid-phase inhibitor of plasmin) with consequent increase in the level of systemic plasmin generation have been observed. This observation is consistent with the intended effect of plasminogen activation. In comparative studies a less than 15% reduction in fibrinogen and a less than 25% reduction in plasminogen were observed in subjects treated with the maximum dose of tenecteplase (10,000 U, corresponding to 50 mg), whereas alteplase caused an approximately 50% decrease in fibrinogen and plasminogen levels. No clinically relevant antibody formation was detected at 30 days.

Clinical effects
Patency data from the phase I and II angiographic studies suggest that tenecteplase, administered as a single intravenous bolus, is effective in dissolving blood clots in the infarct-related artery of subjects experiencing an AMI on a dose related basis.

A large scale mortality trial (ASSENT II) in approx. 17,000 patients showed that tenecteplase is therapeutically equivalent to alteplase in reducing mortality (6.2% for both treatments, at 30 days, upper limit of the 95% CI for the relative risk ratio 1.124) and that the use of tenecteplase is associated with a significantly lower incidence of non-intracranial bleedings (26.4% vs. 28.9%, p=0.0003). This translates into a significantly lower need of transfusions (4.3% vs. 5.5%, p=0.0002). Intracranial haemorrhage occurred at a rate of 0.93% vs. 0.94% for tenecteplase and alteplase, respectively.

Coronary patency and limited clinical outcome data showed that AMI patients have been successfully treated later than 6 hours after symptom onset.

5.2 Pharmacokinetic properties

Tenecteplase is an intravenously administered, recombinant protein that activates plasminogen. Tenecteplase is cleared from circulation by binding to specific receptors in the liver followed by catabolism to small peptides. Binding to hepatic receptors is, however, reduced compared to native t-PA, resulting in a prolonged half-life. Data on tissue distribution and elimination were obtained in studies with radioactively labeled tenecteplase in rats. The main organ to which tenecteplase distributed was the liver. It is not known whether and to what extent tenecteplase binds to plasma proteins in humans.

After single intravenous bolus injection of tenecteplase in patients with acute myocardial infarction, tenecteplase antigen exhibits biphasic elimination from plasma. There is no dose dependence of tenecteplase clearance in the therapeutic dose range. The initial, dominant half life is 24 ± 5.5 (mean +/-SD) min, which is 5 times longer than native t-PA. The terminal half-life is 129 ± 87 min, and plasma clearance is 119 ± 49 ml/min.

Increasing body weight resulted in a moderate increase of tenecteplase clearance, and increasing age resulted in a slight decrease of clearance. Women exhibit in general lower clearance than men, but this can be explained by the generally lower body weight of women.

The effect of renal and hepatic dysfunction on pharmacokinetics of tenecteplase in humans is not known. There is no specific experience to guide the adjustment to tenecteplase dose in patients with hepatic and severe renal insufficiency. However, based on animal data it is not expected that renal dysfunction will affect the pharmacokinetics.

5.3 Preclinical safety data

Intravenous single dose administration in rats, rabbits and dogs resulted only in dose-dependent and reversible alterations of the coagulation parameters with local haemorrhage at the injection site, which was regarded as a consequence of the pharmacodynamic effect of tenecteplase. Multiple-dose toxicity studies in rats and dogs confirmed these above-mentioned observations, but the study duration was limited to two weeks by antibody formation to the human protein tenecteplase, which resulted in anaphylaxis.

Safety pharmacology data in cynomolgus monkeys revealed reduction of blood pressure followed by changes of ECG, but these occurred at exposures that were considerably higher than the clinical exposure.

With regard to the indication and the single dose administration in humans, reproductive toxicity testing was limited to an embryotoxicity study in rabbits, as a sensitive species. Tenecteplase induced total litter deaths during the mid-embryonal period. When tenecteplase was given during the mid- or late-embryonal period maternal animals showed vaginal bleeding on the day after the first dose. Secondary mortality was observed 1-2 days later. Data on the foetal period are not available.

Mutagenicity and carcinogenicity are not expected for this class of recombinant proteins and genotoxicity and carcinogenicity testing were not necessary.

No local irritation of the blood vessel was observed after intravenous, intra-arterial or paravenous administration of the final formulation of tenecteplase.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder: L-arginine, phosphoric acid, polysorbate 20.

Solvent: water for injections

6.2 Incompatibilities

Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG is incompatible with dextrose infusion solutions.

6.3 Shelf life

Shelf life as packaged for sale
2 years

Reconstituted solution
Chemical and physical in-use stability has been demonstrated for up to 24 hours at 30° C.

From a microbiological point of view, the product should be used immediately after reconstitution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8° C.

6.4 Special precautions for storage

Do not store above 30° C. Keep the container in the outer carton.

6.5 Nature and contents of container

20 ml glass vial type I, with a coated (B2-42) grey rubber stopper and a vial cap with integrated reconstitution device of polyethylene filled with powder for solution for injection.
10 ml plasticsyringe pre-filled with 6 ml of water for injections for reconstitution.

6.6 Instructions for use and handling, and disposal

Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG should be reconstituted by adding the complete volume of water for injections from the pre-filled syringe to the vial containing the powder for injection.

1. Ensure that the appropriate vial size is chosen according to the body weight of the patient.

Patients' body weight category (kg)	Volume of reconstituted solution (ml)	Tenecteplase (U)	Tenecteplase (mg)
< 60	6	6,000	30
≥ 60 to < 70	7	7,000	35
≥ 70 to < 80	8	8,000	40
≥ 80 to < 90	9	9,000	45
≥ 90	10	10,000	50

2. Check that the cap of the vial is still intact.
3. Remove the vial cap and connect immediately the pre-filled-syringe to the Luer lock of the Bioset.
4. Place the vial on a firm surface and strongly press down the body of the syringe until a ***"click"*** is noticed. The ***"click"*** confirms the system is activated. Check carefully there is no leakage of fluid. Failure to complete these steps correctly may lead to greater than the required dose of Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG being administered.
5. Add the water for injections into the vial by pushing the syringe plunger slowly down to avoid foaming.

6. Reconstitute by swirling gently.
7. The reconstituted preparation results in a colourless to pale yellow, clear solution. Only clear solution without particles should be used.
8. Directly before the solution will be administered, invert the vial with the syringe still attached, so that the syringe is below the vial.
9. Withdraw into the syringe the appropriate volume of reconstituted solution of Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG, based on the patient's weight.
10. Disconnect the syringe from the vial.
11. Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG is to be administered to the patient, intravenously in about 10 seconds. It should not be administered in a line containing dextrose.
12. Any unused solution should be discarded.

7. MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Strasse 173
D-55216 Ingelheim am Rhein
Germany

8. NUMBER IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/00/168/001
EU/1/00/168/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23 February 2001

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG 8,000 units
Powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG 8,000 units
1 vial contains 8,000 units (40 mg) tenecteplase.
1 prefilled syringe contains 8 ml water for injections.

The reconstituted solution contains 1,000 units (5 mg) tenecteplase per ml.

Potency of tenecteplase is expressed in units (U) by using a reference standard which is specific for tenecteplase and is not comparable with units used for other thrombolytic agents.

Tenecteplase is a recombinant fibrin-specific plasminogen activator.

For excipients, see 6.1.

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Treatment with Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG should be initiated as soon as possible after onset of symptoms.

Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG should be administered on the basis of body weight, with a maximum dose of 10,000 units (50 mg tenecteplase). The volume required to administer the correct dose can be calculated from the following scheme:

Patients' body weight category (kg)	Tenecteplase (U)	Tenecteplase (mg)	Corresponding volume of reconstituted solution (ml)
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The required dose should be administered as a single intravenous bolus over approximately 10 seconds.

A pre-existing intravenous line may be used for administration of Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG in 0.9% sodium chloride solution only. Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG is incompatible with dextrose solution.

No other medicinal product should be added to the injection solution.

Adjunctive therapy
Acetylsalicylic acid (ASA) and heparin should be administered as soon as possible after diagnosis to inhibit the thrombogenic process.

ASA should be administered as soon as possible after AMI symptom onset and continued as long-term treatment. The recommended initial oral dose is between 150 and 325 mg per day. If the patient is unable to ingest tablets, an initial dose of 100-250 mg may be given intravenously if available. The ASA dosage during the following days will be at the discretion of the treating physician.

Heparin should be administered as soon as possible after the diagnosis of AMI has been confirmed, and continued for at least 48 hours on a body weight adjusted basis. For patients weighing 67 kg or less, an initial intravenous heparin bolus not exceeding 4,000 IU is recommended followed initially by not more than an 800 IU/hour infusion. For patients weighing more than 67 kg, an initial intravenous heparin bolus not exceeding 5,000 IU is recommended followed initially by not more than 1,000 IU/hour infusion. For patients already receiving heparin treatment, the initial bolus should not be given. The infusion rate should be adjusted to maintain an aPTT of 50-75 seconds (1.5 to 2.5 times control or a heparin plasma level of 0.2 to 0.5 IU/ml).

4.3 Contraindications

Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG is contraindicated in the following situations because thrombolytic therapy is associated with a higher risk of bleeding:

- Significant bleeding disorder either at present or within the past 6 months
- Patients with current concomitant oral anticoagulant therapy (INR > 1.3)
- Any history of central nervous system damage (i.e. neoplasm, aneurysm, intracranial or spinal surgery)
- Known haemorrhagic diathesis
- Severe uncontrolled hypertension
- Major surgery, biopsy of a parenchymal organ, or significant trauma within the past 2 months
- (this includes any trauma associated with the current AMI)
- Recent trauma to the head or cranium
- Prolonged cardiopulmonary resuscitation (> 2 minutes) within the past 2 weeks
- Acute pericarditis and/or subacute bacterial endocarditis
- Acute pancreatitis

- Severe hepatic dysfunction, including hepatic failure, cirrhosis, portal hypertension (oesophageal varices) and active hepatitis
- Diabetic haemorrhagic retinopathy or other haemorrhagic ophthalmic conditions
- Active peptic ulceration
- Arterial aneurysm and known arterial/venous malformation
- Neoplasm with increased bleeding risk
- Any known history of stroke or transient ischaemic attack or dementia
- Hypersensitivity to the active substance tenecteplase and to any of the excipients

4.4 Special warnings and special precautions for use

Bleeding
The most common complication encountered during Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG therapy is bleeding. The concomitant use of heparin anticoagulation may contribute to bleeding. As fibrin is lysed during Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG therapy, bleeding from recent puncture site may occur. Therefore, thrombolytic therapy requires careful attention to all possible bleeding sites (including catheter insertion sites, arterial and venous puncture sites, cutdown sites and needle puncture sites). The use of rigid catheters as well as intramuscular injections and non-essential handling of the patient should be avoided during treatment with Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG.

Most frequently haemorrhage at the injection site, and occasionally genitourinary and gingival bleeding were observed.

Should serious bleeding occur, in particular cerebral haemorrhage, concomitant heparin administration should be terminated immediately. Administration of protamine should be considered if heparin has been administered within 4 hours before the onset of bleeding. In the few patients who fail to respond to these conservative measures, judicious use of transfusion products may be indicated. Transfusion of cryoprecipitate, fresh frozen plasma, and platelets should be considered with clinical and laboratory reassessment after each administration. A target fibrinogen level of 1 g/l is desirable with cryoprecipitate infusion. Antifibrinolytic agents are available as a last alternative. The use of Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG therapy has to be carefully evaluated in order to balance the potential risks with anticipated benefits under the following conditions:

- Systolic blood pressure > 160 mm Hg
- Cerebrovascular disease
- Recent gastrointestinal or genitourinary bleeding (within the past 10 days)
- High likelihood of left heart thrombus, e.g., mitral stenosis with atrial fibrillation
- Any known recent (within the past 2 days) intramuscular injection
- Advanced age, i.e. over 75 years
- Low body weight < 60 kg

Arrhythmias
Coronary thrombolysis may result in arrhythmias associated with reperfusion. It is recommended that antiarrhythmic therapy for bradycardia and/or ventricular tachyarrhythmias (pacemaker, defibrillator) be available when Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG is administered.

GPIIb/IIIa antagonists
There is no experience with the use of GPIIb/IIIa antagonists within the first 24 hours after start of treatment.

Re-administration
Since at present there is no experience with re-administration of Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG, the re-administration is not recommended. However, no antibody formation to the tenecteplase molecule has been observed. If an anaphylactoid reaction occurs, the injection should be discontinued immediately and appropriate therapy should be initiated. In any case,

tenecteplase should not be re-administered before assessment of haemostatic factors like fibrinogen, plasminogen and alpha2-antiplasmin.

4.5 Interaction with other medicinal products and other forms of interaction

No formal interaction studies with Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG and medicinal products commonly administered in patients with AMI have been performed. However, the analysis of data from more than 12,000 patients treated during phase I, II and III did not reveal any clinically relevant interactions with medicinal products commonly used in patients with AMI and concomitantly used with Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG.

Medicinal products that affect coagulation or those that alter platelet function may increase the risk of bleeding prior to, during or after Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG therapy.

4.6 Pregnancy and lactation

No experience in pregnant women is available for tenecteplase. Because animal studies (see also section 5.3.) have shown a high risk of vaginal bleeding presumably from the placenta and of pregnancy loss, the benefit of treatment has to be evaluated against the potential risks which may aggravate an acute life-threatening situation.

It is not known if tenecteplase is excreted into breast milk. Breast milk should be discarded within the first 24 hours after thrombolytic therapy.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Haemorrhage
Haemorrhage is a very common undesirable effect associated with the use of tenecteplase. The type of haemorrhage is predominantly superficial at the injection site. Ecchymoses are observed commonly but usually do not require any specific action. Commonly, (< 10%) gastro-intestinal or genitourinary bleeding and epistaxis occurred. Pulmonary haemorrhage, retroperitoneal bleedings and cerebral haemorrhage were uncommonly observed (< 1%). Haemopericardium occured rarely. Death and permanent disability are reported in patients who have experienced stroke (including intracranial bleeding) and other serious bleeding episodes. Blood transfusions were rarely required.

Cardiovascular
As with other thrombolytic agents, the following events have been reported as sequelae of myocardial infarction and/or thrombolytic administration:

- very common (>10%): hypotension, heart rate and rhythm disorders, angina pectoris
- common (>1%, <10%): recurrent ischaemia, heart failure, reinfarction, cardiogenic shock, pericarditis, pulmonary oedema
- uncommon (>0.1%, <1%): cardiac arrest, mitral insufficiency, pericardial effusion, venous thrombosis, cardiac tamponade, myocardial rupture
- rare (>0.01%, <0.1%): pulmonary embolism

Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG therapy may lead to crystal cholesterol embolisation in very rare cases or uncommonly to thrombotic embolism in very rare cases.

These cardiovascular events can be life-threatening and may lead to death.

Nervous system
Isolated cases of events related to the nervous system (e.g. somnolence, aphasia, convulsion) have been reported. Ischaemic or haemorrhagic cerebrovascular events may be contributing or underlying conditions.

Anaphylactoid Reaction
Anaphylactoid reactions (e.g. rash, urticaria, laryngeal oedema) have been rarely reported.

Other
Nausea and/or vomiting and fever were commonly reported and are most frequent of the remaining adverse events.

4.9 Overdose

In the event of overdose there may be an increased risk of bleeding. In case of severe prolonged bleeding substitution therapy may be considered (plasma, platelets), see also section 4.4.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antithrombotic agents, ATC code: B01A D

Mechanism of action
Tenecteplase is a recombinant fibrin-specific plasminogen activator that is derived from native t-PA by modifications at three sites of the protein structure. It binds to the fibrin component of the thrombus (blood clot) and selectively converts thrombus-bound plasminogen to plasmin, which degrades the fibrin matrix of the thrombus. Tenecteplase has a higher fibrin specificity and greater resistance to inactivation by its endogenous inhibitor (PAI-1) compared to native t-PA.

Pharmacodynamic effects
After administration of tenecteplase dose dependent consumption of α2-antiplasmin (the fluid-phase inhibitor of plasmin) with consequent increase in the level of systemic plasmin generation have been observed. This observation is consistent with the intended effect of plasminogen activation. In comparative studies a less than 15% reduction in fibrinogen and a less than 25% reduction in plasminogen were observed in subjects treated with the maximum dose of tenecteplase (10,000 U, corresponding to 50 mg), whereas alteplase caused an approximately 50% decrease in fibrinogen and plasminogen levels. No clinically relevant antibody formation was detected at 30 days.

Clinical effects
Patency data from the phase I and II angiographic studies suggest that tenecteplase, administered as a single intravenous bolus, is effective in dissolving blood clots in the infarct-related artery of subjects experiencing an AMI on a dose related basis.

A large scale mortality trial (ASSENT II) in approx. 17,000 patients showed that tenecteplase is therapeutically equivalent to alteplase in reducing mortality (6.2% for both treatments, at 30 days, upper limit of the 95% CI for the relative risk ratio 1.124) and that the use of tenecteplase is associated with a significantly lower incidence of non-intracranial bleedings (26.4% vs. 28.9%, p=0.0003). This translates into a significantly lower need of transfusions (4.3% vs. 5.5%, p=0.0002). Intracranial haemorrhage occurred at a rate of 0.93% vs. 0.94% for tenecteplase and alteplase, respectively.

Coronary patency and limited clinical outcome data showed that AMI patients have been successfully treated later than 6 hours after symptom onset.

5.2 Pharmacokinetic properties

Tenecteplase is an intravenously administered, recombinant protein that activates plasminogen. Tenecteplase is cleared from circulation by binding to specific receptors in the liver followed by catabolism to small peptides. Binding to hepatic receptors is, however, reduced compared to native t-PA, resulting in a prolonged half-life. Data on tissue distribution and elimination were obtained in studies with radioactively labeled tenecteplase in rats. The main organ to which tenecteplase distributed was the liver. It is not known whether and to what extent tenecteplase binds to plasma proteins in humans.

After single intravenous bolus injection of tenecteplase in patients with acute myocardial infarction, tenecteplase antigen exhibits biphasic elimination from plasma. There is no dose dependence of tenecteplase clearance in the therapeutic dose range. The initial, dominant half life is 24 ± 5.5 (mean +/-SD) min, which is 5 times longer than native t-PA. The terminal half-life is 129 ± 87 min, and plasma clearance is 119 ± 49 ml/min.

Increasing body weight resulted in a moderate increase of tenecteplase clearance, and increasing age resulted in a slight decrease of clearance. Women exhibit in general lower clearance than men, but this can be explained by the generally lower body weight of women.

The effect of renal and hepatic dysfunction on pharmacokinetics of tenecteplase in humans is not known. There is no specific experience to guide the adjustment to tenecteplase dose in patients with hepatic and severe renal insufficiency. However, based on animal data it is not expected that renal dysfunction will affect the pharmacokinetics.

5.3 Preclinical safety data

Intravenous single dose administration in rats, rabbits and dogs resulted only in dose-dependent and reversible alterations of the coagulation parameters with local haemorrhage at the injection site, which was regarded as a consequence of the pharmacodynamic effect of tenecteplase. Multiple-dose toxicity studies in rats and dogs confirmed these above-mentioned observations, but the study duration was limited to two weeks by antibody formation to the human protein tenecteplase, which resulted in anaphylaxis.

Safety pharmacology data in cynomolgus monkeys revealed reduction of blood pressure followed by changes of ECG, but these occurred at exposures that were considerably higher than the clinical exposure.

With regard to the indication and the single dose administration in humans, reproductive toxicity testing was limited to an embryotoxicity study in rabbits as a sensitive species. Tenecteplase induced total litter deaths during the mid-embryonal period. When tenecteplase was given during the mid- or late-embryonal period maternal animals showed vaginal bleeding on the day after the first dose. Secondary mortality was observed 1-2 days later. Data on the foetal period are not available.

Mutagenicity and carcinogenicity are not expected for this class of recombinant proteins and genotoxicity and carcinogenicity testing were not necessary.

No local irritation of the blood vessel was observed after intravenous, intra-arterial or paravenous administration of the final formulation of tenecteplase.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder: L-arginine, phosphoric acid, polysorbate 20.

Solvent: water for injections

6.2 Incompatibilities

Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG is incompatible with dextrose infusion solutions.

6.3 Shelf life

Shelf life as packaged for sale
2 years

Reconstituted solution
Chemical and physical in-use stability has been demonstrated for up to 24 hours at 30° C.

From a microbiological point of view, the product should be used immediately after reconstitution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8° C.

6.4 Special precautions for storage

Do not store above 30° C. Keep the container in the outer carton.

6.5 Nature and contents of container

20 ml glass vial type I, with a coated (B2-42) grey rubber stopper and a vial cap with integrated reconstitution device of polyethylene filled with powder for solution for injection.
10 ml plastic syringe pre-filled with 8 ml of water for injections for reconstitution.

6.6 Instructions for use and handling, and disposal

Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG should be reconstituted by adding the complete volume of water for injections from the pre-filled syringe to the vial containing the powder for injection.

1. Ensure that the appropriate vial size is chosen according to the body weight of the patient.

Patients' body weight category (kg)	Volume of reconstituted solution (ml)	Tenecteplase (U)	Tenecteplase (mg)
< 60	6	6,000	30
≥ 60 to < 70	7	7,000	35
≥ 70 to < 80	8	8,000	40
≥ 80 to < 90	9	9,000	45
≥ 90	10	10,000	50

2. Check that the cap of the vial is still intact.
3. Remove the vial cap and connect immediately the pre-filled-syringe to the Luer lock of the Bioset.
4. Place the vial on a firm surface and strongly press down the body of the syringe until a ***"click"*** is noticed. The ***"click"*** confirms the system is activated. Check carefully there is no leakage of fluid. Failure to complete these steps correctly may lead to greater than the required dose of Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG being administered.
5. Add the water for injections into the vial by pushing the syringe plunger slowly down to avoid foaming.

6. Reconstitute by swirling gently.
7. The reconstituted preparation results in a colourless to pale yellow, clear solution. Only clear solution without particles should be used.
8. Directly before the solution will be administered, invert the vial with the syringe still attached, so that the syringe is below the vial.
9. Withdraw into the syringe the appropriate volume of reconstituted solution of Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG, based on the patient's weight.
10. Disconnect the syringe from the vial.
11. Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG is to be administered to the patient, intravenously in about 10 seconds. It should not be administered in a line containing dextrose.
12. Any unused solution should be discarded.

7. MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Strasse 173
D-55216 Ingelheim am Rhein
Germany

8. NUMBER IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/00/168/002
EU/1/00/168/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23 February 2001

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG 10,000 units
Powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG 10,000 units
1 vial contains 10,000 units (50 mg) tenecteplase.
1 prefilled syringe contains 10 ml water for injections.

The reconstituted solution contains 1,000 units (5 mg) tenecteplase per ml.

Potency of tenecteplase is expressed in units (U) by using a reference standard which is specific for tenecteplase and is not comparable with units used for other thrombolytic agents.

Tenecteplase is a recombinant fibrin-specific plasminogen activator.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

The powder is white to off-white.

The reconstituted preparation results in a colourless to pale yellow, clear solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG is indicated for the thrombolytic treatment of suspected myocardial infarction with persistent ST elevation or recent left Bundle Branch Block within 6 hours after the onset of acute myocardial infarction (AMI) symptoms.

4.2 Posology and method of administration

Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG should be prescribed by physicians experienced in the use of thrombolytic treatment and with the facilities to monitor that use.

Treatment with Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG should be initiated as soon as possible after onset of symptoms.

Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG should be administered on the basis of body weight, with a maximum dose of 10,000 units (50 mg tenecteplase). The volume required to administer the correct dose can be calculated from the following scheme:

Patients' body weight category (kg)	Tenecteplase (U)	Tenecteplase (mg)	Corresponding volume of reconstituted solution (ml)
< 60	6,000	30	6
≥ 60 to < 70	7,000	35	7
≥ 70 to < 80	8,000	40	8
≥ 80 to < 90	9,000	45	9
≥ 90	10,000	50	10
see section 6.6.: Instructions for use and handling			

The required dose should be administered as a single intravenous bolus over approximately 10 seconds.

A pre-existing intravenous line may be used for administration of Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG in 0.9% sodium chloride solution only. Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG is incompatible with dextrose solution.

No other medicinal product should be added to the injection solution.

Adjunctive therapy
Acetylsalicylic acid (ASA) and heparin should be administered as soon as possible after diagnosis to inhibit the thrombogenic process.

ASA should be administered as soon as possible after AMI symptom onset and continued as long-term treatment. The recommended initial oral dose is between 150 and 325 mg per day. If the patient is unable to ingest tablets, an initial dose of 100-250 mg may be given intravenously if available. The ASA dosage during the following days will be at the discretion of the treating physician.

Heparin should be administered as soon as possible after the diagnosis of AMI has been confirmed, and continued for at least 48 hours on a body weight adjusted basis. For patients weighing 67 kg or less, an initial intravenous heparin bolus not exceeding 4,000 IU is recommended followed initially by not more than an 800 IU/hour infusion. For patients weighing more than 67 kg, an initial intravenous heparin bolus not exceeding 5,000 IU is recommended followed initially by not more than 1,000 IU/hour infusion. For patients already receiving heparin treatment, the initial bolus should not be given. The infusion rate should be adjusted to maintain an aPTT of 50-75 seconds (1.5 to 2.5 times control or a heparin plasma level of 0.2 to 0.5 IU/ml).

4.3 Contraindications

Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG is contraindicated in the following situations because thrombolytic therapy is associated with a higher risk of bleeding:

- Significant bleeding disorder either at present or within the past 6 months
- Patients with current concomitant oral anticoagulant therapy (INR > 1.3)
- Any history of central nervous system damage (i.e. neoplasm, aneurysm, intracranial or spinal surgery)
- Known haemorrhagic diathesis
- Severe uncontrolled hypertension
- Major surgery, biopsy of a parenchymal organ, or significant trauma within the past 2 months
- (this includes any trauma associated with the current AMI)
- Recent trauma to the head or cranium
- Prolonged cardiopulmonary resuscitation (> 2 minutes) within the past 2 weeks
- Acute pericarditis and/or subacute bacterial endocarditis
- Acute pancreatitis

- Severe hepatic dysfunction, including hepatic failure, cirrhosis, portal hypertension (oesophageal varices) and active hepatitis
- Diabetic haemorrhagic retinopathy or other haemorrhagic ophthalmic conditions
- Active peptic ulceration
- Arterial aneurysm and known arterial/venous malformation
- Neoplasm with increased bleeding risk
- Any known history of stroke or transient ischaemic attack or dementia
- Hypersensitivity to the active substance tenecteplase and to any of the excipients

4.4 Special warnings and special precautions for use

Bleeding
The most common complication encountered during Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG therapy is bleeding. The concomitant use of heparin anticoagulation may contribute to bleeding. As fibrin is lysed during Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG therapy, bleeding from recent puncture site may occur. Therefore, thrombolytic therapy requires careful attention to all possible bleeding sites (including catheter insertion sites, arterial and venous puncture sites, cutdown sites and needle puncture sites). The use of rigid catheters as well as intramuscular injections and non-essential handling of the patient should be avoided during treatment with Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG.

Most frequently haemorrhage at the injection site, and occasionally genitourinary and gingival bleeding were observed.

Should serious bleeding occur, in particular cerebral haemorrhage, concomitant heparin administration should be terminated immediately. Administration of protamine should be considered if heparin has been administered within 4 hours before the onset of bleeding. In the few patients who fail to respond to these conservative measures, judicious use of transfusion products may be indicated. Transfusion of cryoprecipitate, fresh frozen plasma, and platelets should be considered with clinical and laboratory reassessment after each administration. A target fibrinogen level of 1 g/l is desirable with cryoprecipitate infusion. Antifibrinolytic agents are available as a last alternative. The use of Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG therapy has to be carefully evaluated in order to balance the potential risks with anticipated benefits under the following conditions:

- Systolic blood pressure > 160 mm Hg
- Cerebrovascular disease
- Recent gastrointestinal or genitourinary bleeding (within the past 10 days)
- High likelihood of left heart thrombus, e.g., mitral stenosis with atrial fibrillation
- Any known recent (within the past 2 days) intramuscular injection
- Advanced age, i.e. over 75 years
- Low body weight < 60 kg

Arrhythmias
Coronary thrombolysis may result in arrhythmias associated with reperfusion. It is recommended that antiarrhythmic therapy for bradycardia and/or ventricular tachyarrhythmias (pacemaker, defibrillator) be available when Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG is administered.

GPIIb/IIIa antagonists
There is no experience with the use of GPIIb/IIIa antagonists within the first 24 hours after start of treatment.

Re-administration
Since at present there is no experience with re-administration of Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG, the re-administration is not recommended. However, no antibody formation to the tenecteplase molecule has been observed. If an anaphylactoid reaction occurs, the injection should be discontinued immediately and appropriate therapy should be initiated. In any case,

tenecteplase should not be re-administered before assessment of haemostatic factors like fibrinogen, plasminogen and alpha2-antiplasmin.

4.5. Interaction with other medicinal products and other forms of interaction

No formal interaction studies with Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG and medicinal products commonly administered in patients with AMI have been performed. However, the analysis of data from more than 12,000 patients treated during phase I, II and III did not reveal any clinically relevant interactions with medicinal products commonly used in patients with AMI and concomitantly used with Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG.

Medicinal products that affect coagulation or those that alter platelet function (e.g. ticlopidine, clopidogrel, LMWH) may increase the risk of bleeding prior to, during or after Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG therapy.

4.6 Pregnancy and lactation

No experience in pregnant women is available for tenecteplase. Because animal studies (see also section 5.3.) have shown a high risk of vaginal bleeding presumably from the placenta and of pregnancy loss, the benefit of treatment has to be evaluated against the potential risks which may aggravate an acute life-threatening situation.

It is not known if tenecteplase is excreted into breast milk. Breast milk should be discarded within the first 24 hours after thrombolytic therapy.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Haemorrhage
Haemorrhage is a very common undesirable effect associated with the use of tenecteplase. The type of haemorrhage is predominantly superficial at the injection site. Ecchymoses are observed commonly but usually do not require any specific action. Commonly, (< 10%) gastro-intestinal or genitourinary bleeding and epistaxis occurred. Pulmonary haemorrhage, retroperitoneal bleedings and cerebral haemorrhage were uncommonly observed (< 1%). Haemopericardium occured rarely. Death and permanent disability are reported in patients who have experienced stroke (including intracranial bleeding) and other serious bleeding episodes. Blood transfusions were rarely required.

Cardiovascular
As with other thrombolytic agents, the following events have been reported as sequelae of myocardial infarction and/or thrombolytic administration:

- very common (>10%): hypotension, heart rate and rhythm disorders, angina pectoris
- common (>1%, <10%): recurrent ischaemia, heart failure, reinfarction, cardiogenic shock, pericarditis, pulmonary oedema
- uncommon (>0.1%, <1%): cardiac arrest, mitral insufficiency, pericardial effusion, venous thrombosis, cardiac tamponade, myocardial rupturerare
- rare (>0.01%, <0.1%): pulmonary embolism

Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG therapy may lead to crystal cholesterol embolisation in very rare cases or uncommonly to thrombotic embolism.

These cardiovascular events can be life-threatening and may lead to death.

Nervous system
Isolated cases of events related to the nervous system (e.g. somnolence, aphasia, convulsion) have been reported. Ischaemic or haemorrhagic cerebrovascular events may be contributing or underlying conditions.

Anaphylactoid Reaction
Anaphylactoid reactions (e.g. rash, urticaria, laryngeal oedema) have been rarely reported.

Other
Nausea and/or vomiting and fever were commonly reported and are most frequent of the remaining adverse events.

4.9 Overdose

In the event of overdose there may be an increased risk of bleeding. In case of severe prolonged bleeding substitution therapy may be considered (plasma, platelets), see also section 4.4.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antithrombotic agents, ATC code: B01A D

Mechanism of action
Tenecteplase is a recombinant fibrin-specific plasminogen activator that is derived from native t-PA by modifications at three sites of the protein structure. It binds to the fibrin component of the thrombus (blood clot) and selectively converts thrombus-bound plasminogen to plasmin, which degrades the fibrin matrix of the thrombus. Tenecteplase has a higher fibrin specificity and greater resistance to inactivation by its endogenous inhibitor (PAI-1) compared to native t-PA.

Pharmacodynamic effects
After administration of tenecteplase dose dependent consumption of α2-antiplasmin (the fluid-phase inhibitor of plasmin) with consequent increase in the level of systemic plasmin generation have been observed. This observation is consistent with the intended effect of plasminogen activation. In comparative studies a less than 15% reduction in fibrinogen and a less than 25% reduction in plasminogen were observed in subjects treated with the maximum dose of tenecteplase (10,000 U, corresponding to 50 mg), whereas alteplase caused an approximately 50% decrease in fibrinogen and plasminogen levels. No clinically relevant antibody formation was detected at 30 days.

Clinical effects
Patency data from the phase I and II angiographic studies suggest that tenecteplase, administered as a single intravenous bolus, is effective in dissolving blood clots in the infarct-related artery of subjects experiencing an AMI on a dose related basis.

A large scale mortality trial (ASSENT II) in approx. 17,000 patients showed that tenecteplase is therapeutically equivalent to alteplase in reducing mortality (6.2% for both treatments, at 30 days, upper limit of the 95% CI for the relative risk ratio 1.124) and that the use of tenecteplase is associated with a significantly lower incidence of non-intracranial bleedings (26.4% vs. 28.9%, p=0.0003). This translates into a significantly lower need of transfusions (4.3% vs. 5.5%, p=0.0002). Intracranial haemorrhage occurred at a rate of 0.93% vs. 0.94% for tenecteplase and alteplase, respectively.

Coronary patency and limited clinical outcome data showed that AMI patients have been successfully treated later than 6 hours after symptom onset.

5.2 Pharmacokinetic properties

Tenecteplase is an intravenously administered, recombinant protein that activates plasminogen. Tenecteplase is cleared from circulation by binding to specific receptors in the liver followed by catabolism to small peptides. Binding to hepatic receptors is, however, reduced compared to native t-PA, resulting in a prolonged half-life. Data on tissue distribution and elimination were obtained in studies with radioactively labeled tenecteplase in rats. The main organ to which tenecteplase distributed was the liver. It is not known whether and to what extent tenecteplase binds to plasma proteins in humans.

After single intravenous bolus injection of tenecteplase in patients with acute myocardial infarction, tenecteplase antigen exhibits biphasic elimination from plasma. There is no dose dependence of tenecteplase clearance in the therapeutic dose range. The initial, dominant half life is 24 ± 5.5 (mean +/-SD) min, which is 5 times longer than native t PA. The terminal half-life is 129 ± 87 min, and plasma clearance is 119 ± 49 ml/min.

Increasing body weight resulted in a moderate increase of tenecteplase clearance, and increasing age resulted in a slight decrease of clearance. Women exhibit in general lower clearance than men, but this can be explained by the generally lower body weight of women.

The effect of renal and hepatic dysfunction on pharmacokinetics of tenecteplase in humans is not known. There is no specific experience to guide the adjustment to tenecteplase dose in patients with hepatic and severe renal insufficiency. However, based on animal data it is not expected that renal dysfunction will affect the pharmacokinetics.

5.3 Preclinical safety data

Intravenous single dose administration in rats, rabbits and dogs resulted only in dose-dependent and reversible alterations of the coagulation parameters with local haemorrhage at the injection site, which was regarded as a consequence of the pharmacodynamic effect of tenecteplase. Multiple-dose toxicity studies in rats and dogs confirmed these above-mentioned observations, but the study duration was limited to two weeks by antibody formation to the human protein tenecteplase, which resulted in anaphylaxis.

Safety pharmacology data in cynomolgus monkeys revealed reduction of blood pressure followed by changes of ECG, but these occurred at exposures that were considerably higher than the clinical exposure.

With regard to the indication and the single dose administration in humans, reproductive toxicity testing was limited to an embryotoxicity study in rabbits, as a sensitive species. Tenecteplase induced total litter deaths during the mid-embryonal period. When tenecteplase was given during the mid- or late-embryonal period maternal animals showed vaginal bleeding on the day after the first dose. Secondary mortality was observed 1-2 days later. Data on the foetal period are not available.

Mutagenicity and carcinogenicity are not expected for this class of recombinant proteins and genotoxicity and carcinogenicity testing were not necessary.

No local irritation of the blood vessel was observed after intravenous, intra-arterial or paravenous administration of the final formulation of tenecteplase.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder: L-arginine, phosphoric acid, polysorbate 20.

Solvent: water for injections

6.2 Incompatibilities

Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG is incompatible with dextrose infusion solutions.

6.3 Shelf life

Shelf life as packaged for sale
2 years

Reconstituted solution
Chemical and physical in-use stability has been demonstrated for up to 24 hours at 30° C.

From a microbiological point of view, the product should be used immediately after reconstitution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8° C.

6.4 Special precautions for storage

Do not store above 30° C. Keep the container in the outer carton.

6.5 Nature and contents of container

20 ml glass vial type I, with a coated (B2-42) grey rubber stopper and a vial cap with integrated reconstitution device of polyethylene filled with powder for solution for injection.
10 ml plastic syringe pre-filled with 10 ml of water for injections for reconstitution.

6.6 Instructions for use and handling, and disposal

Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG should be reconstituted by adding the complete volume of water for injections from the pre-filled syringe to the vial containing the powder for injection.

1. Ensure that the appropriate vial size is chosen according to the body weight of the patient.

Patients' body weight category (kg)	Volume of reconstituted solution (ml)	Tenecteplase (U)	Tenecteplase (mg)
< 60	6	6,000	30
≥ 60 to < 70	7	7,000	35
≥ 70 to < 80	8	8,000	40
≥ 80 to < 90	9	9,000	45
≥ 90	10	10,000	50

2. Check that the cap of the vial is still intact.
3. Remove the vial cap and connect immediately the pre-filled-syringe to the Luer lock of the Bioset.
4. Place the vial on a firm surface and strongly press down the body of the syringe until a ***"click"*** is noticed. The ***"click"*** confirms the system is activated. Check carefully there is no leakage of fluid. Failure to complete these steps correctly may lead to greater than the required dose of Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG being administered.
5. Add the water for injections into the vial by pushing the syringe plunger slowly down to avoid foaming.

6. Reconstitute by swirling gently.
7. The reconstituted preparation results in a colourless to pale yellow, clear solution. Only clear solution without particles should be used.
8. Directly before the solution will be administered, invert the vial with the syringe still attached, so that the syringe is below the vial.
9. Withdraw into the syringe the appropriate volume of reconstituted solution of Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG, based on the patient's weight.
10. Disconnect the syringe from the vial.
11. Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG is to be administered to the patient, intravenously in about 10 seconds. It should not be administered in a line containing dextrose.
12. Any unused solution should be discarded.

7. MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Strasse 173
D-55216 Ingelheim am Rhein
Germany

8. NUMBER IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/00/168/003
EU/1/00/168/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23 February 2001

10. DATE OF REVISION OF THE TEXT

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B CONDITIONS OF THE MARKETING AUTHORISATION

A MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance
Boehringer Ingelheim Pharma GmbH & Co.KG
Binkendorferstr. 65
88397 Biberach/Riss
Germany

Name and address of the manufacturer responsible for batch release
Boerhinger Ingelheim Pharma GmbH & Co.KG
Binkendorferstr. 65
88397 Biberach/Riss
Germany

B CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, 4.2).

- **OTHER CONDITIONS**

The holder of this marketing authorisation must inform the European Commission about the marketing plans for the medicinal product authorised by this decision.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

A. PARTICULARS TO APPEAR ON THE CARTON LABEL (PP) SYRINGE

1. NAME OF THE MEDICINAL PRODUCT

Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG 6,000 U
Powder and solvent for solution for injection
Tenecteplase

2. STATEMENT OF ACTIVE SUBSTANCE(S)

6,000 U tenecteplase per vial

When reconstituted with 6 ml water for injections each ml contains 1,000 U tenecteplase

3. LIST OF EXCIPIENTS

Excipients: L-Arginine, Phosphoric Acid, Polysorbate 20

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder for solution for injection
1 pre-filled syringe of solvent for parenteral use

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

For intravenous use after reconstitution with 6 ml solvent

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Please follow accurately the instructions for use. Failure to do so may lead to greater than the required dose of Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG being administered.

8. EXPIRY DATE

EXP {month/year}

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C
Keep the container in the outer carton in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Strasse 173
D-55216 Ingelheim am Rhein
Germany

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/00/168/001

13. MANUFACTURER'S BATCH NUMBER

Batch {number}

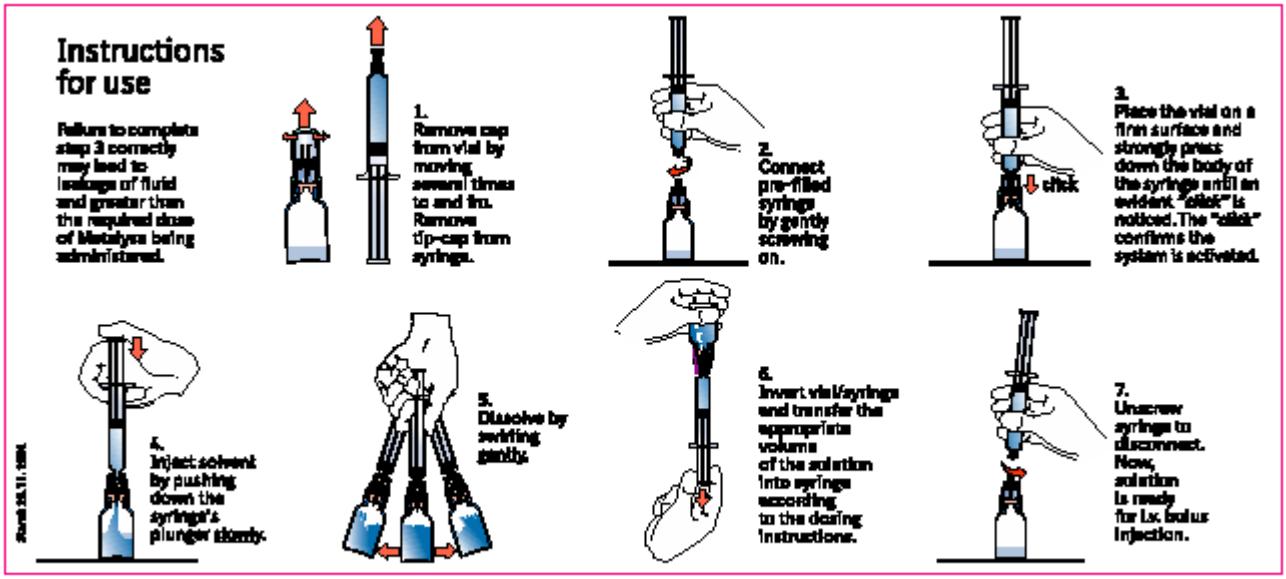
14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

For single use only. After reconstitution the product should be used immediately. Any unused solution should be discarded. Only clear solution without particles should be used. Read the leaflet for information on reconstitution and dose to be administered.

PARTICULARS TO APPEAR ON THE INNER SIDE OF THE LID OF THE CARTON IN FORM OF A PICTOGRAMM



PARTICULARS TO APPEAR ON THE CARTON LABEL (CYCLOOLEFINE-COPOLYMER) SYRINGE

1. NAME OF THE MEDICINAL PRODUCT

Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG 6,000 U
Powder and solvent for solution for injection
Tenecteplase

2. STATEMENT OF ACTIVE SUBSTANCE(S)

6,000 U tenecteplase per vial

When reconstituted with 6 ml water for injections each ml contains 1,000 U tenecteplase

3. LIST OF EXCIPIENTS

Excipients: L-Arginine, Phosphoric Acid, Polysorbate 20

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder for solution for injection
1 pre-filled syringe of solvent for parenteral use

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

For intravenous use after reconstitution with 6 ml solvent

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Please follow accurately the instructions for use. Failure to do so may lead to greater than the required dose of Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG being administered.

8. EXPIRY DATE

EXP {month/year}

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C
Keep the container in the outer carton in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Strasse 173
D-55216 Ingelheim am Rhein
Germany

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/0/00/000/000

13. MANUFACTURER'S BATCH NUMBER

Batch {number}

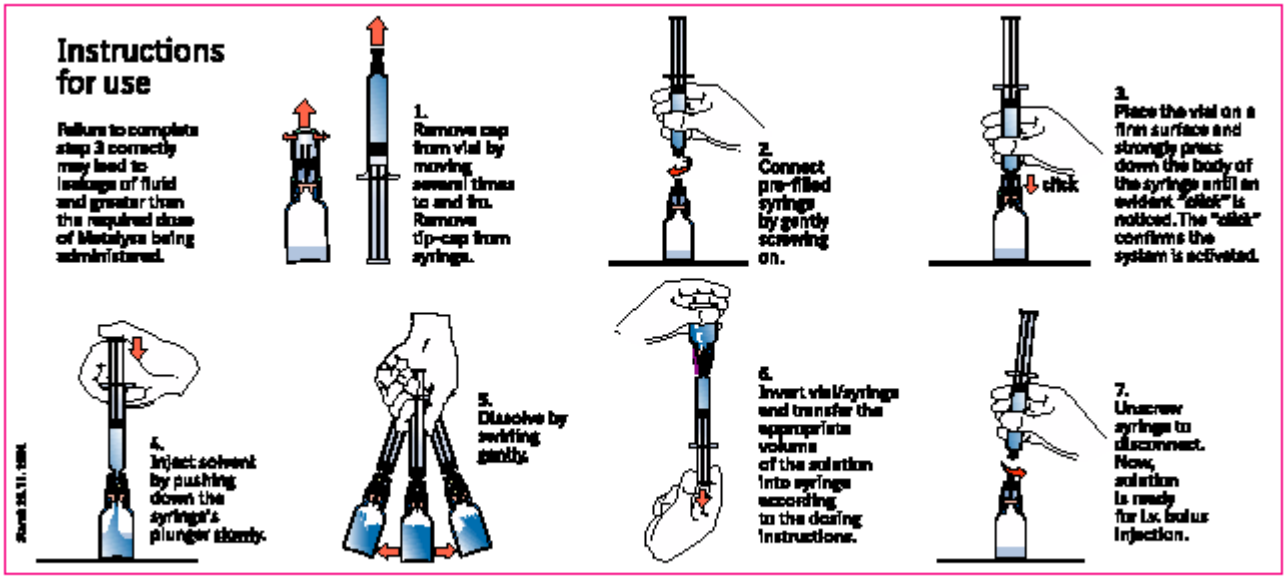
14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

For single use only. After reconstitution the product should be used immediately. Any unused solution should be discarded. Only clear solution without particles should be used. Read the leaflet for information on reconstitution and dose to be administered.

PARTICULARS TO APPEAR ON THE INNER SIDE OF THE LID OF THE CARTON IN FORM OF A PICTOGRAMM



PARTICULARS TO APPEAR ON THE VIAL LABEL

VIAL LABEL FOR POWDER FOR SOLUTION FOR INJECTION

1. NAME OF THE MEDICINAL PRODUCT

Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG 6,000 U
Powder for solution for injection.
Tenecteplase

2. STATEMENT OF ACTIVE SUBSTANCE(S)

6,000 U tenecteplase per vial

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

For intravenous use after reconstitution with 6 ml solvent

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {month/year}

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C
Keep the container in the outer carton

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

13. MANUFACTURER'S BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

Read the package leaflet before use

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SYRINGE LABEL FOR SOLVENT

1. NAME OF THE MEDICINAL PRODUCT AND IF NECESSARY ROUTE(S) OF ADMINISTRATION

Solvent for Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG 6,000 U
Solvent for parenteral use

2. METHOD OF ADMINISTRATION

Reconstituted solution, for patients of body weight (kg):

3. EXPIRY DATE

EXP {month/year}

4. BATCH NUMBER

Batch {number}

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6 ml water for injections

PARTICULARS TO APPEAR ON THE CARTON LABEL (PP) SYRINGE

1. NAME OF THE MEDICINAL PRODUCT

Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG 8,000 U
Powder and solvent for solution for injection
Tenecteplase

2. STATEMENT OF ACTIVE SUBSTANCE(S)

8,000 U tenecteplase per vial

When reconstituted with 8 ml water for injections each ml contains 1,000 U tenecteplase

3. LIST OF EXCIPIENTS

Excipients: L-Arginine, Phosphoric Acid, Polysorbate 20

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder for solution for injection
1 pre-filled syringe of solvent for parenteral use

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

For intravenous use after reconstitution with 8 ml solvent

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Please follow accurately the instructions for use. Failure to do so may lead to greater than the required dose of Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG being administered.

8. EXPIRY DATE

EXP {month/year}

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C
Keep the container in the outer carton in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Strasse 173
D-55216 Ingelheim am Rhein
Germany

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/00/168/002

13. MANUFACTURER'S BATCH NUMBER

Batch {number}

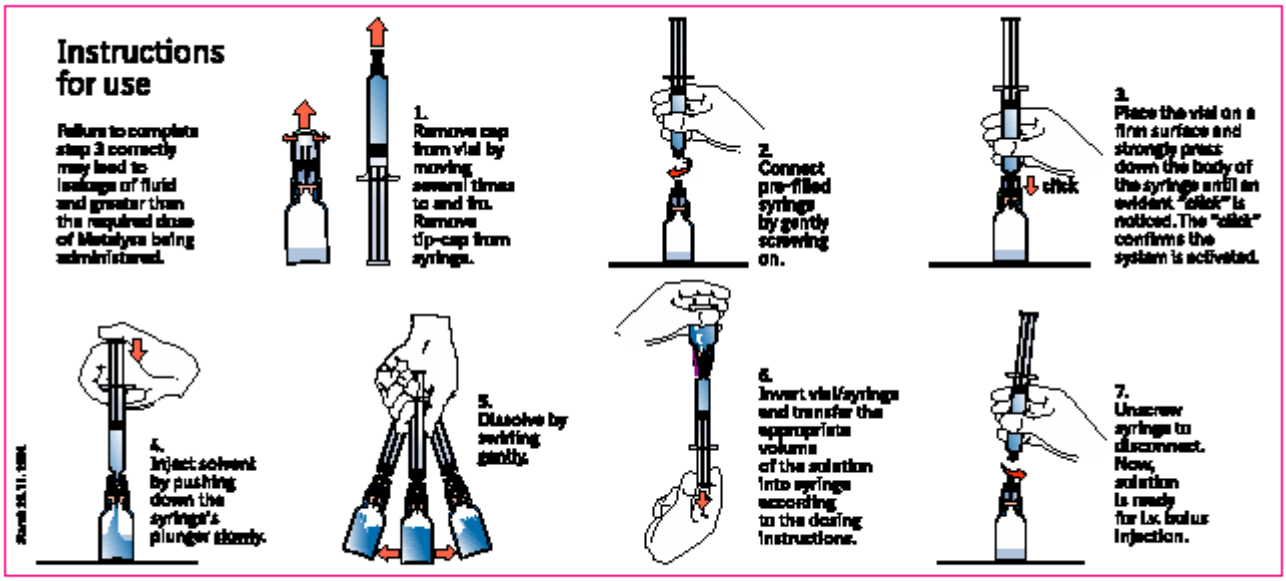
14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

For single use only. After reconstitution the product should be used immediately. Any unused solution should be discarded. Only clear solution without particles should be used. Read the leaflet for information on reconstitution and dose to be administered.

PARTICULARS TO APPEAR ON THE INNER SIDE OF THE LID OF THE CARTON IN FORM OF A PICTOGRAMM



PARTICULARS TO APPEAR ON THE CARTON LABEL (CYCLOOLEFINE-COPOLYMER) SYRINGE

1. NAME OF THE MEDICINAL PRODUCT

Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG 8,000 U
Powder and solvent for solution for injection
Tenecteplase

2. STATEMENT OF ACTIVE SUBSTANCE(S)

8,000 U tenecteplase per vial

When reconstituted with 8 ml water for injections each ml contains 1,000 U tenecteplase

3. LIST OF EXCIPIENTS

Excipients: L-Arginine, Phosphoric Acid, Polysorbate 20

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder for solution for injection
1 pre-filled syringe of solvent for parenteral use

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

For intravenous use after reconstitution with 8 ml solvent

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Please follow accurately the instructions for use. Failure to do so may lead to greater than the required dose of Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG being administered.

8. EXPIRY DATE

EXP {month/year}

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C
Keep the container in the outer carton in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Strasse 173
D-55216 Ingelheim am Rhein
Germany

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/0/00/000/000

13. MANUFACTURER'S BATCH NUMBER

Batch {number}

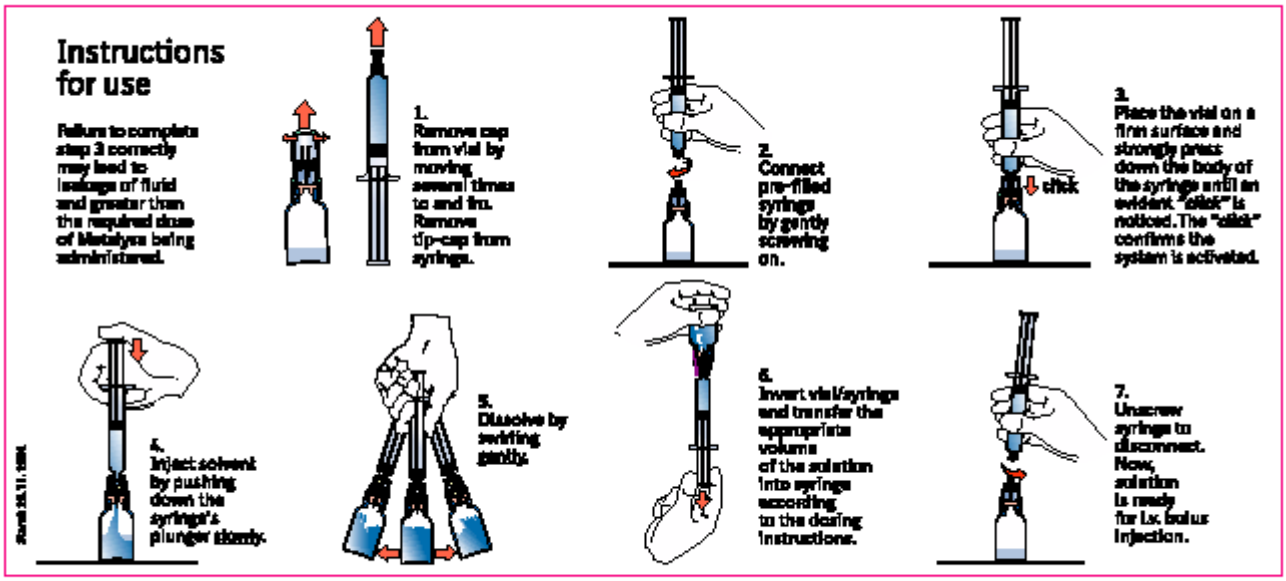
14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

For single use only. After reconstitution the product should be used immediately. Any unused solution should be discarded. Only clear solution without particles should be used. Read the leaflet for information on reconstitution and dose to be administered.

PARTICULARS TO APPEAR ON THE INNER SIDE OF THE LID OF THE CARTON IN FORM OF A PICTOGRAMM



PARTICULARS TO APPEAR ON THE VIAL LABEL

VIAL LABEL FOR POWDER FOR SOLUTION FOR INJECTION

1. NAME OF THE MEDICINAL PRODUCT

Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG 8,000 U
Powder for solution for injection.
Tenecteplase

2. STATEMENT OF ACTIVE SUBSTANCE(S)

8,000 U tenecteplase per vial

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

For intravenous use after reconstitution with 8 ml solvent

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {month/year}

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C
Keep the container in the outer carton

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

13. MANUFACTURER'S BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

Read the package leaflet before use

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SYRINGE LABEL FOR SOLVENT

1. NAME OF THE MEDICINAL PRODUCT AND IF NECESSARY ROUTE(S) OF ADMINISTRATION

Solvent for Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG 8,000 U
Solvent for parenteral use

2. METHOD OF ADMINISTRATION

Reconstituted solution, for patients of body weight (kg):

3. EXPIRY DATE

EXP {month/year}

4. BATCH NUMBER

Batch {number}

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

8 ml water for injections

PARTICULARS TO APPEAR ON THE CARTON LABEL (PP) SYRINGE

1. NAME OF THE MEDICINAL PRODUCT

Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG 10,000 U
Powder and solvent for solution for injection
Tenecteplase

2. STATEMENT OF ACTIVE SUBSTANCE(S)

10,000 U tenecteplase per vial

When reconstituted with 10 ml water for injections each ml contains 1,000 U tenecteplase

3. LIST OF EXCIPIENTS

Excipients: L-Arginine, Phosphoric Acid, Polysorbate 20

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder for solution for injection
1 pre-filled syringe of solvent for parenteral use

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

For intravenous use after reconstitution with 10 ml solvent

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Please follow accurately the instructions for use. Failure to do so may lead to greater than the required dose of Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG being administered.

8. EXPIRY DATE

EXP {month/year}

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C
Keep the container in the outer carton in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Strasse 173
D-55216 Ingelheim am Rhein
Germany

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/00/168/003

13. MANUFACTURER'S BATCH NUMBER

Batch {number}

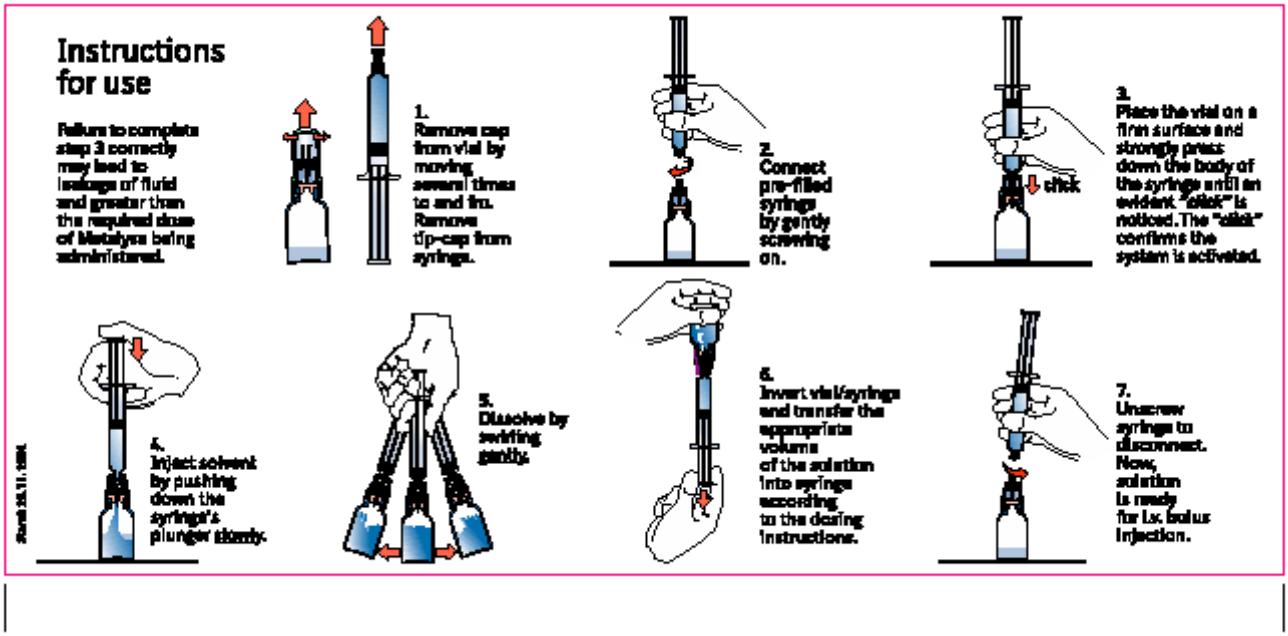
14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

For single use only. After reconstitution the product should be used immediately. Any unused solution should be discarded. Only clear solution without particles should be used. Read the leaflet for information on reconstitution and dose to be administered.

PARTICULARS TO APPEAR ON THE INNER SIDE OF THE LID OF THE CARTON IN FORM OF A PICTOGRAMM



PARTICULARS TO APPEAR ON THE CARTON LABEL (CYCLOOLEFINE-COPOLYMER) SYRINGE

1. NAME OF THE MEDICINAL PRODUCT

Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG 10,000 U
Powder and solvent for solution for injection
Tenecteplase

2. STATEMENT OF ACTIVE SUBSTANCE(S)

10,000 U tenecteplase per vial

When reconstituted with 10 ml water for injections each ml contains 1,000 U tenecteplase

3. LIST OF EXCIPIENTS

Excipients: L-Arginine, Phosphoric Acid, Polysorbate 20

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder for solution for injection
1 pre-filled syringe of solvent for parenteral use

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

For intravenous use after reconstitution with 10 ml solvent

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Please follow accurately the instructions for use. Failure to do so may lead to greater than the required dose of Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG being administered.

8. EXPIRY DATE

EXP {month/year}

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C
Keep the container in the outer carton in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Strasse 173
D-55216 Ingelheim am Rhein
Germany

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/0/00/000/000

13. MANUFACTURER'S BATCH NUMBER

Batch {number}

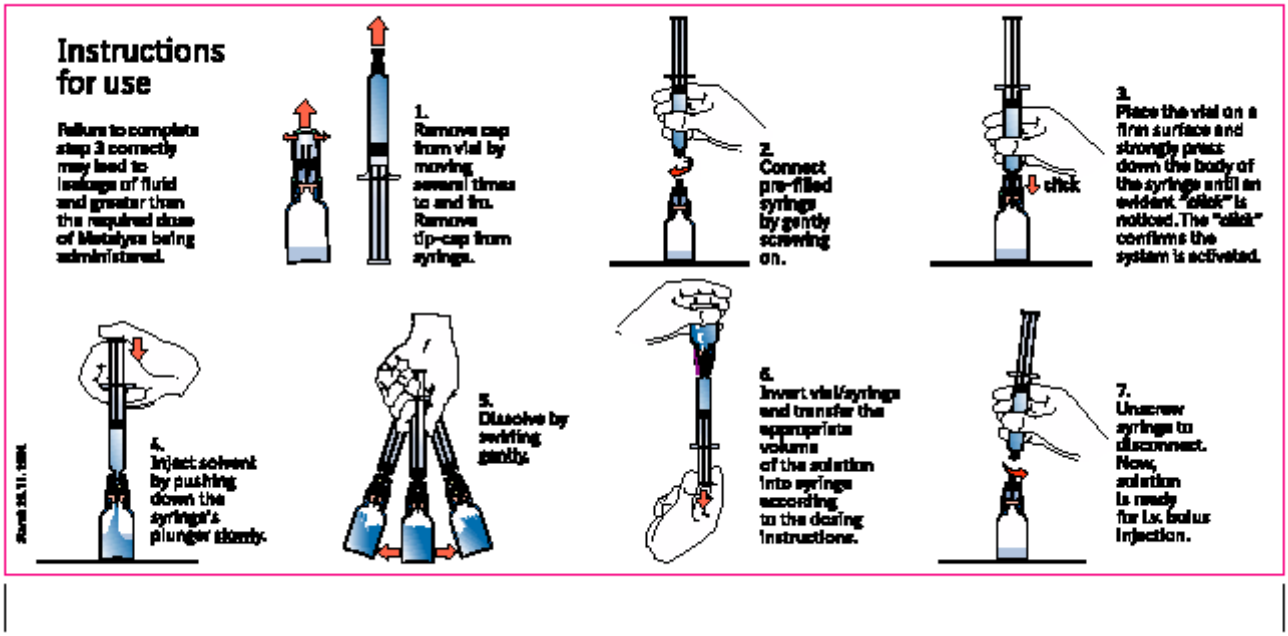
14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

For single use only. After reconstitution the product should be used immediately. Any unused solution should be discarded. Only clear solution without particles should be used. Read the leaflet for information on reconstitution and dose to be administered.

PARTICULARS TO APPEAR ON THE INNER SIDE OF THE LID OF THE CARTON IN FORM OF A PICTOGRAMM



PARTICULARS TO APPEAR ON THE VIAL LABEL

VIAL LABEL FOR POWDER FOR SOLUTION FOR INJECTION

1. NAME OF THE MEDICINAL PRODUCT

Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG 10,000 U
Powder for solution for injection.
Tenecteplase

2. STATEMENT OF ACTIVE SUBSTANCE(S)

10,000 U tenecteplase per vial

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

For intravenous use after reconstitution with 10 ml solvent

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {month/year}

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C
Keep the container in the outer carton

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

13. MANUFACTURER'S BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

Read the package leaflet before use

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SYRINGE LABEL FOR SOLVENT

1. NAME OF THE MEDICINAL PRODUCT AND IF NECESSARY ROUTE(S) OF ADMINISTRATION

Solvent for Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG 10,000 U
Solvent for parenteral use

2. METHOD OF ADMINISTRATION

Reconstituted solution, for patients of body weight (kg):

3. EXPIRY DATE

EXP {month/year}

4. BATCH NUMBER

Batch {number}

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 ml water for injections

B. PACKAGE LEAFLET

PACKAGE LEAFLET

Read all of this leaflet
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.

In this leaflet:

TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG 6,000 units powder and solvent for solution for injection
Tenecteplase

- The active substance is tenecteplase. One vial contains 6,000 units of tenecteplase. One pre-filled syringe contains 6 ml of water for injections.
- The other ingredients are L-arginine, phosphoric acid and polysorbate 20.
- The TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG solvent is water for injections.

Marketing Authorisation Holder:

Boehringer Ingelheim International GmbH
Binger Strasse 173
D-55216 Ingelheim am Rhein
Germany

Manufacturer:

Boehringer Ingelheim Pharma KG
Birkendorferstrasse 65
D-88397 Biberach/Riss
Germany

1. WHAT TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG IS AND WHAT IT IS USED FOR

TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG is a powder and solvent for solution for injection. This means that each pack contains:

- one vial of 6,000 units TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG powder and one pre-filled syringe containing 6 ml water for injections

Before use, the solvent (water for injections) is added to the powder to form a solution that is given by injection.

TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG belongs to a group of medicines called thrombolytic agents. These medicines help to dissolve blood clots. Tenecteplase is a recombinant fibrin-specific plasminogen activator.

TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG is used to treat myocardial infarctions (heart attacks) within 6 hours after the onset of symptoms and helps to dissolve the blood clots that have formed in the blood vessels of the heart. This helps to prevent the damage caused by heart attacks and has been shown to save lives.

2. BEFORE YOU RECEIVE TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG

TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG will not be prescribed and given by your doctor

- if you have, or have recently had, an illness that increases your risk of bleeding (haemorrhage), including:
  - ❖ a bleeding disorder or tendency to bleed (haemorrhage)
  - ❖ stroke (cerebrovascular event)
  - ❖ very high, uncontrolled blood pressure
  - ❖ a head injury
  - ❖ severe liver disease
  - ❖ **a disorder affecting the blood vessels in the eye (e.g. diabetic haemorrhagic retinopathy)**
  - ❖ a stomach ulcer (peptic ulcer)
  - ❖ varicose veins in the gullet (oesophageal varices)
  - ❖ abnormality of the blood vessels (e.g. an aneurysm)
  - ❖ certain tumours
  - ❖ inflammation of the lining around the heart (pericarditis); inflammation or infection of the heart valves (endocarditis);
- if you are taking tablets/capsules used to ”thin” the blood, such as warfarin or coumarin (anti-coagulants);
- if you have an inflamed pancreas (pancreatitis);
- if you have recently had major surgery including surgery to your brain or spine;
- if you have been given cardiopulmonary resuscitation (chest compressions) for more than 2 minutes duration, in the last two weeks;
- if you are hypersensitive to tenecteplase or any of the other ingredients in TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG.

Your doctor will take special care with TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG:

- if you have high blood pressure;
- if you have problems with circulation of blood in the brain (cerebrovascular disease);
- if you have had gastrointestinal (gut) or genitourinary bleeding within the last ten days (this may cause blood in stools or urine);
- if you have a heart valve abnormality (e.g. mitral stenosis) with an abnormal heart rhythm (e.g. atrial fibrillation);
- if you have had an intramuscular injection in the last two days;
- if you are aged over 75 years;
- if you weigh less than 60 kg.

Pregnancy
If you are pregnant ask your doctor for advice before you are given TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG.

Breast-feeding

If you are breast-feeding ask your doctor for advice before you are given TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG.

Taking other medicines
Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

3. HOW TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG IS ADMINISTERED

The doctor calculates your dose of TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG according to your bodyweight, based on the following scheme:

Bodyweight (kg)	less than 60	60 to 70	70 to 80	80 to 90	above 90
Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG (U)	6,000	7,000	8,000	9,000	10,000

Your doctor will give you acetylsalicylic acid and heparin injections in addition to TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG, as soon as possible after your chest pain starts.

TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG is given by a single injection into a vein by a doctor who is experienced in the use of this type of drug.

Your doctor will give TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG as soon as possible after your chest pain starts as a single dose.

Repetition is not recommended.

4. POSSIBLE SIDE EFFECTS

Like all medicines, TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG can have side effects.

The following side effects are very common (>10%) with TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG:

- low blood pressure (hypotension)
- irregular heart beat
- chest pain (angina pectoris)
- bleeding where the injection is given

The following side effects are common (>1%, <10%) with TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG:

- nausea
- vomiting
- fever
- nosebleeds
- further heart attach or chest pain (recurrent ischaemia, reinfarction)
- heart failure

- shock due to heart failure
- inflammation of the lining around the heart (pericarditis)
- fluid in the lungs (pulmonary oedema)
- genitourinary bleeding (you may notice blood in your urine)
- bruising
- gastro-intestinal bleeding (bleeding from the stomach or bowel)

The following side effects are uncommon (>0.1%, <1%), but have been reported following treatment with TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG:

- cardiac arrest
- problem with the heart valve or heart lining (mitral insufficiency, pericardial effusion)
- blood clot in the vein (venous thrombosis)
- fluid between heart lining and the heart (cardiac tamponade)
- rupture in heart muscle
- internal bleeding in the abdomen (retroperitoneal bleeding)
- bleeding in the brain (cerebral haemorrhage). Death or permanent disability may occur following bleeding in the brain or other serious bleeding events
- bleeding in the lungs (pulmonary haemorrhage)
- hypersensitivity (anaphylactoid reactions) e.g. rash, hives (urticaria), swelling of the throat

The following side effects have occurred rarely (>0.01%, <0.1%) after treatment with TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG:

- bleeding into the area surrounding the heart (haemopericardium)
- blood clot in the lung (pulmonary embolism)
- blood clot in the blood vessels

In rare cases (>0.01%, <0.1%) Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG therapy may lead to crystal cholesterol clots.

Tell your doctor immediately if you think you are experiencing any of these side effects.

Isolated cases of events related to the nervous system have been reported e.g. drowsiness (somnolence), speech disorders and fits (convulsions).

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG

Keep out of the reach and sight of children.

Do not store above 30° C. Keep the container in the outer carton in order to protect from light.

Once Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG has been reconstituted it may be stored for up to 24 hours at 30°C. However, for microbiological reasons your doctor will normally use the reconstituted solution for injection immediately.

TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG will not be used after the expiry date stated on the label/carton.

This leaflet was last approved on {date}

Further Information
For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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PACKAGE LEAFLET

Read all of this leaflet
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.

In this leaflet:

TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG 8,000 units powder and solvent for solution for injection
Tenecteplase

- The active substance is tenecteplase. One vial contains 8,000 units of tenecteplase. One pre-filled syringe contains 8 ml of water for injections.
- The other ingredients are L-arginine, phosphoric acid and polysorbate 20.
- The TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG solvent is water for injections.

Marketing Authorisation Holder:

Boehringer Ingelheim International GmbH
Binger Strasse 173
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Manufacturer:

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Germany

1. WHAT TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG IS AND WHAT IT IS USED FOR

TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG is a powder and solvent for solution for injection. This means that each pack contains:

- one vial of 8,000 units TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG powder and one pre-filled syringe containing 8 ml water for injections

Before use, the solvent (water for injections) is added to the powder to form a solution that is given by injection.

TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG belongs to a group of medicines called thrombolytic agents. These medicines help to dissolve blood clots. Tenecteplase is a recombinant fibrin-specific plasminogen activator.

TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG is used to treat myocardial infarctions (heart attacks) within 6 hours after the onset of symptoms and helps to dissolve the blood clots that have formed in the blood vessels of the heart. This helps to prevent the damage caused by heart attacks and has been shown to save lives.

2. BEFORE YOU RECEIVE TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG

TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG will not be prescribed and given by your doctor

- if you have, or have recently had, an illness that increases your risk of bleeding (haemorrhage), including:
  - ❖ a bleeding disorder or tendency to bleed (haemorrhage)
  - ❖ stroke (cerebrovascular event)
  - ❖ very high, uncontrolled blood pressure
  - ❖ a head injury
  - ❖ severe liver disease
  - ❖ **a disorder affecting the blood vessels in the eye (e.g. diabetic haemorrhagic retinopathy)**
  - ❖ a stomach ulcer (peptic ulcer)
  - ❖ varicose veins in the gullet (oesophageal varices)
  - ❖ abnormality of the blood vessels (e.g. an aneurysm)
  - ❖ certain tumours
  - ❖ inflammation of the lining around the heart (pericarditis); inflammation or infection of the heart valves (endocarditis);
- if you are taking tablets/capsules used to ”thin” the blood, such as warfarin or coumarin (anti-coagulants);
- if you have an inflamed pancreas (pancreatitis);
- if you have recently had major surgery including surgery to your brain or spine;
- if you have been given cardiopulmonary resuscitation (chest compressions) for more than 2 minutes duration, in the last two weeks;
- if you are hypersensitive to tenecteplase or any of the other ingredients in TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG.

Your doctor will take special care with TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG:

- if you have high blood pressure;
- if you have problems with circulation of blood in the brain (cerebrovascular disease);
- if you have had gastrointestinal (gut) or genitourinary bleeding within the last ten days (this may cause blood in stools or urine);
- if you have a heart valve abnormality (e.g. mitral stenosis) with an abnormal heart rhythm (e.g. atrial fibrillation);
- if you have had an intramuscular injection in the last two days;
- if you are aged over 75 years;
- if you weigh less than 60 kg.

Pregnancy
If you are pregnant ask your doctor for advice before you are given TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG.

Breast-feeding

If you are breast-feeding ask your doctor for advice before you are given TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG.

Taking other medicines
Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

3. HOW TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG IS ADMINISTERED

The doctor calculates your dose of TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG according to your bodyweight, based on the following scheme:

Bodyweight (kg)	less than 60	60 to 70	70 to 80	80 to 90	above 90
Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG (U)	6,000	7,000	8,000	9,000	10,000

Your doctor will give you acetylsalicylic acid and heparin injections in addition to TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG, as soon as possible after your chest pain starts.

TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG is given by a single injection into a vein by a doctor who is experienced in the use of this type of drug.

Your doctor will give TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG as soon as possible after your chest pain starts as a single dose.

Repetition is not recommended.

4. POSSIBLE SIDE EFFECTS

Like all medicines, TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG can have side effects.

The following side effects are very common (>10%) with TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG:

- low blood pressure (hypotension)
- irregular heart beat
- chest pain (angina pectoris)
- bleeding where the injection is given

The following side effects are common (>1%, <10%) with TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG:

- nausea
- vomiting
- fever
- nosebleeds
- further heart attach or chest pain (recurrent ischaemia, reinfarction)
- heart failure

- shock due to heart failure
- inflammation of the lining around the heart (pericarditis)
- fluid in the lungs (pulmonary oedema)
- genitourinary bleeding (you may notice blood in your urine)
- bruising
- gastro-intestinal bleeding (bleeding from the stomach or bowel)

The following side effects are uncommon (>0.1%, <1%), but have been reported following treatment with TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG:

- cardiac arrest
- problem with the heart valve or heart lining (mitral insufficiency, pericardial effusion)
- blood clot in the vein (venous thrombosis)
- fluid between heart lining and the heart (cardiac tamponade)
- rupture in heart muscle
- internal bleeding in the abdomen (retroperitoneal bleeding)
- bleeding in the brain (cerebral haemorrhage). Death or permanent disability may occur following bleeding in the brain or other serious bleeding events
- bleeding in the lungs (pulmonary haemorrhage)
- hypersensitivity (anaphylactoid reactions) e.g. rash, hives (urticaria), swelling of the troat

The following side effects have occurred rarely (>0.01%, <0.1%) after treatment with TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG:

- bleeding into the area surrounding the heart (haemopericardium)
- blood clot in the lung (pulmonary embolism)
- blood clot in the blood vessels

In rare cases (>0.01%, <0.1%) Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG therapy may lead to crystal cholesterol clots.

Isolated cases of events related to the nervous system have been reported e.g. drowsiness (somnolence), speech disorders and fits (convulsions).

Tell your doctor immediately if you think you are experiencing any of these side effects.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG

Keep out of the reach and sight of children.

Do not store above 30° C. Keep the container in the outer carton in order to protect from light.

Once Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG has been reconstituted it may be stored for up to 24 hours at 30°C. However, for microbiological reasons your doctor will normally use the reconstituted solution for injection immediately.

TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG will not be used after the expiry date stated on the label/carton.

This leaflet was last approved on {date}

Further Information
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PACKAGE LEAFLET

Read all of this leaflet
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.

In this leaflet:

TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG 10,000 units powder and solvent for solution for injection
Tenecteplase

- The active substance is tenecteplase. One vial contains 10,000 units of tenecteplase. One pre-filled syringe contains 10 ml of water for injections.
- The other ingredients are L-arginine, phosphoric acid and polysorbate 20.
- The TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG solvent is water for injections.

Marketing Authorisation Holder:

Boehringer Ingelheim International GmbH
Binger Strasse 173
D-55216 Ingelheim am Rhein
Germany

Manufacturer:

Boehringer Ingelheim Pharma KG
Birkendorferstrasse 65
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Germany

1. WHAT TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG IS AND WHAT IT IS USED FOR

TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG is a powder and solvent for solution for injection. This means that each pack contains:

- one vial of 10,000 units TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG powder and one pre-filled syringe containing 10 ml water for injections.

Before use, the solvent (water for injections) is added to the powder to form a solution that is given by injection.

TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG belongs to a group of medicines called thrombolytic agents. These medicines help to dissolve blood clots. Tenecteplase is a recombinant fibrin-specific plasminogen activator.

TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG is used to treat myocardial infarctions (heart attacks) within 6 hours after the onset of symptoms and helps to dissolve the blood clots that have formed in the blood vessels of the heart. This helps to prevent the damage caused by heart attacks and has been shown to save lives.

2. BEFORE YOU RECEIVE TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG

TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG will not be prescribed and given by your doctor

- if you have, or have recently had, an illness that increases your risk of bleeding (haemorrhage), including:
  - ❖ a bleeding disorder or tendency to bleed (haemorrhage)
  - ❖ stroke (cerebrovascular event)
  - ❖ very high, uncontrolled blood pressure
  - ❖ a head injury
  - ❖ severe liver disease
  - ❖ **a disorder affecting the blood vessels in the eye (e.g. diabetic haemorrhagic retinopathy)**
  - ❖ a stomach ulcer (peptic ulcer)
  - ❖ varicose veins in the gullet (oesophageal varices)
  - ❖ abnormality of the blood vessels (e.g. an aneurysm)
  - ❖ certain tumours
  - ❖ inflammation of the lining around the heart (pericarditis); inflammation or infection of the heart valves (endocarditis);
- if you are taking tablets/capsules used to ”thin” the blood, such as warfarin or coumarin (anti-coagulants);
- if you have an inflamed pancreas (pancreatitis);
- if you have recently had major surgery including surgery to your brain or spine;
- if you have been given cardiopulmonary resuscitation (chest compressions) for more than 2 minutes duration, in the last two weeks;
- if you are hypersensitive to tenecteplase or any of the other ingredients in TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG.

Your doctor will take special care with TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG:

- if you have high blood pressure;
- if you have problems with circulation of blood in the brain (cerebrovascular disease);
- if you have had gastrointestinal (gut) or genitourinary bleeding within the last ten days (this may cause blood in stools or urine);
- if you have a heart valve abnormality (e.g. mitral stenosis) with an abnormal heart rhythm (e.g. atrial fibrillation);
- if you have had an intramuscular injection in the last two days;
- if you are aged over 75 years;
- if you weigh less than 60 kg.

Pregnancy
If you are pregnant ask your doctor for advice before you are given TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG.

Breast-feeding

If you are breast-feeding ask your doctor for advice before you are given TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG.

Taking other medicines
Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

3. HOW TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG IS ADMINISTERED

The doctor calculates your dose of TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG according to your bodyweight, based on the following scheme:

Bodyweight (kg)	less than 60	60 to 70	70 to 80	80 to 90	above 90
Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG (U)	6,000	7,000	8,000	9,000	10,000

Your doctor will give you acetylsalicylic acid and heparin injections in addition to TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG, as soon as possible after your chest pain starts.

TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG is given by a single injection into a vein by a doctor who is experienced in the use of this type of drug.

Your doctor will give TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG as soon as possible after your chest pain starts as a single dose.

Repetition is not recommended.

4. POSSIBLE SIDE EFFECTS

Like all medicines, TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG can have side effects.

The following side effects are very common (>10%) with TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG:

- low blood pressure (hypotension)
- irregular heart beat
- chest pain (angina pectoris)
- bleeding where the injection is given

The following side effects are common (>1%, <10%) with TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG:

- nausea
- vomiting
- fever
- nosebleeds
- further heart attach or chest pain (recurrent ischaemia, reinfarction)
- heart failure

- shock due to heart failure
- inflammation of the lining around the heart (pericarditis)
- fluid in the lungs (pulmonary oedema)
- genitourinary bleeding (you may notice blood in your urine)
- bruising
- gastro-intestinal bleeding (bleeding from the stomach or bowel)

The following side effects are uncommon (>0.1%, <1%), but have been reported following treatment with TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG:

- cardiac arrest
- problem with the heart valve or heart lining (mitral insufficiency, pericardial effusion)
- blood clot in the vein (venous thrombosis)
- fluid between heart lining and the heart (cardiac tamponade)
- rupture in heart muscle
- internal bleeding in the abdomen (retroperitoneal bleeding)
- bleeding in the brain (cerebral haemorrhage). Death or permanent disability may occur following bleeding in the brain or other serious bleeding events
- bleeding in the lungs (pulmonary haemorrhage)
- hypersensitivity (anaphylactoid reactions) e.g. rash, hives (urticaria), swelling of the troat

The following side effects have occurred rarely (>0.01%, <0.1%) after treatment with TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG:

- bleeding into the area surrounding the heart (haemopericardium)
- blood clot in the lung (pulmonary embolism)
- blood clot in the blood vessels

In rare cases (>0.01%, <0.1%) Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG therapy may lead to crystal cholesterol clots.

Isolated cases of events related to the nervous system have been reported e.g. drowsiness (somnolence), speech disorders and fits (convulsions).

Tell your doctor immediately if you think you are experiencing any of these side effects.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG

Keep out of the reach and sight of children.

Do not store above 30° C. Keep the container in the outer carton in order to protect from light.

Once Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG has been reconstituted it may be stored for up to 24 hours at 30°C. However, for microbiological reasons your doctor will normally use the reconstituted solution for injection immediately.

TENECTEPLASE BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG will not be used after the expiry date stated on the label/carton.

This leaflet was last approved on {date}

Further Information
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